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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/284,180	06/09/1999	TORU KIMURA	20-4546P	1992

2292 7590 01/14/2002

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EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 01/14/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No. 09/284,180	Applicant(s) KIMURA ET AL.	
	Examiner Shin-Lin Chen	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34,41-43,45,48-52 and 54* is/are pending in the application.

4a) Of the above claim(s) *54* is/are withdrawn from consideration.

5)☒ Claim(s) *34,41,42,51 and 52* is/are allowed.

6)☒ Claim(s) *43,45 and 48-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on **11-20-01** has been entered.

Applicants' preliminary amendment filed 11-20-01 has been entered. Claims 34, 41-43, 45, 48 and 51 have been amended. Claims 35-40, 44, 46, 47, 53 and 55 have been canceled. Claims 34, 41-43, 45, 48-52 and 54 are pending. Claims 34, 41-43, 45 and 48-52 are under consideration.

It should be noted that claim 54 is withdrawn from consideration by examiner because it is distinct from the elected invention, i.e. group I, according to the Official action mailed 8-9-00 (Paper No. 13). Claim 54 and group I are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MEP. § 806.05(h)). In the instant case the polynucleotide sequences of semaphorin W, SEQ ID No. 2, 5 and 10, can be used to produce proteins by using cell culture. The polynucleotide sequences set forth above or their complementary sequences can be used as a probe to detect the presence of target nucleic acid molecule in a sample. A method of producing a protein by using cell culture

and a method of detecting a target nucleic acid molecule in a sample are materially different processes. Thus, claim 54 and the elected invention, group I, are patentably distinct.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 43, 45 and 48-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims read on an isolated nucleic acid **comprising** a polynucleotide having a nucleotide sequence that is at least **80%** identical to the nucleotide sequence of SEQ ID No. 1 or 2, or is at least 80% identical to a nucleotide sequence encoding SEQ ID No. 3, and said nucleic acid encodes a protein having the biological activity of inhibiting neurite outgrowth from dorsal root ganglion or collapsing growth cones of retinal ganglion cells.

The claims encompass various nucleic acids having unknown nucleotide sequences adding to 5', 3' and/or within the sequence of SEQ ID No. 1 or 2, or a nucleotide sequence encoding SEQ ID No. 3. The specification of the present application only disclosed the nucleotide sequences of SEQ ID Nos. 1 and 2 (rat semaphorin) and the amino acid sequence

deduced from SEQ ID No. 2 (SEQ ID No. 3), and the nucleotide sequences of human semaphorin cDNA (SEQ ID Nos. 4, 5, 7 and 10).

The scope of the claims includes various unknown and unidentified nucleic acids encoding a genus of numerous structural variants of the disclosed semaphorin protein (SEQ ID No. 3), and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification only discloses the homologies of the primary amino acid sequences in semaphorin domain among the known semaphorin genes are 20-80% and not necessarily high (specification, page 4, lines 17-20), and suggest that the amino acid residue at position 204 of SEQ ID No. 3 could be essential to the activity of semaphorin protein (specification, page 18, lines 17-22). The post-filing documents accompanied with the preliminary amendment filed 11-20-01 indicates that the full length human semaphorin cDNA sequence is 82.4% identical to the rat semaphorin cDNA sequence and the overall degree of amino acid sequence identity is 90.6%, and methods for making variant nucleic acids as claimed in claims 43 and 45 and assays for identifying protein having the claimed biological activity were known in the art (amendment, p. 13, 14). The presented data are not found persuasive because nucleotide sequence of SEQ ID Nos. 1 and 2 contains 4008 bases and 2331 bases, respectively, and 20% variation of SEQ ID Nos. 1 and 2 would account for about 800 bases and 466 bases differences, respectively. The claimed nucleic acids could vary dramatically from the disclosed nucleotide sequences of the present application. Although the human semaphorin cDNA is 82.4% identical to rat semaphorin W cDNA and the method for making variant nucleic acids and

assays for identifying protein having the claimed biological activity were known in the art, the scope of the claims encompasses unknown and unidentified genes having nucleotide sequence that is at least 80% identical to SEQ ID No. 1 or 2 but do not have the claimed biological activity. The specification fails to provide sufficient description that applicants had possession of the full scope of the nucleic acids at the time of the invention.

Further, as discussed in the preceding Official action mailed 5-24-01 (Paper No. 21), the specification indicates the ""semaphorin domain" refers to a domain consisting of 300-600 amino acid residues more than 20% of which are identical to those amino acids constituting the semaphorin domain of any one of ten known semaphorins" and thirteen cysteines are conserved in semaphorin domain of the ten known semaphorins (Specification, page 23, lines 10-13 and 22-24). The amino acid sequences between semaphorin domains of the known semaphorins could differ from 240-480 amino acid residues which account to 720-1440 nucleotide difference among the known semaphorin domains. The identical amino acid residues among semaphorin domains of the known semaphorin are not necessarily identical throughout all known semaphorin rather they are identical to a certain subgroups of the known semaphorins. No common structural feature of the nucleic acids that encode the semaphorin domain has been disclosed in the specification except the consensus cysteine residues. Thus, one skilled in the art at the time of the invention would not know how to distinguish the nucleic acid encoding semaphorin protein from the nucleic acid encoding other proteins. This limited information is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of all the nucleic

acids encoding variants of the semaphorin W disclosed in the present invention. Thus it is concluded that the written description requirement is not satisfied for the nucleic acids that encode the genus of proteins discussed above.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the disclosed SEQ ID Nos. 1, 2, 4, 5, 7 and 10, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicants argue that the full length human semaphorin cDNA sequence is 82.4% identical to the rat semaphorin cDNA sequence and the overall degree of amino acid sequence identity is 90.6%, and methods for making variant nucleic acids as claimed in claims 43 and 45 and assays for identifying protein having the claimed biological activity were known in the art (amendment, p. 13, 14). Applicants further argue that the degree of sequence variation among avian and mammalian semaphorin W genes is typically more than 80% (amendment, p. 15). This is not found persuasive because of the reasons set forth above in the 112 first written description section.

3. Claims 43, 45 and 48-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated DNA comprising SEQ ID No. 1 or 2 and a DNA encoding a polypeptide sequence of SEQ ID No. 3 that functions to inhibit neurite outgrowth, does not reasonably provide enablement for any isolated nucleic acid comprising a polynucleotide having a nucleotide sequence that is at least 80% identical to SEQ ID No. 1 or 2, or a nucleotide sequence encoding SEQ ID No. 3, and said nucleic acid encodes a protein having

the biological activity of inhibiting neurite outgrowth from dorsal root ganglion or collapsing growth cones of retinal ganglion cells, an expression plasmid comprising said nucleic acid, a host cell comprising said expression plasmid, and a process for producing a recombinant protein by using said host cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to an isolated nucleic acid **comprising** a polynucleotide having a nucleotide sequence that is at least **80%** identical to the nucleotide sequence of SEQ ID No. 1 or 2, or is at least 80% identical to a nucleotide sequence encoding SEQ ID No. 3, wherein said nucleic acid encodes a protein having the biological activity of inhibiting neurite outgrowth from dorsal root ganglion or collapsing growth cones of retinal ganglion cells; an expression plasmid comprising said nucleic acid, a host cell comprising said expression plasmid, and a process for producing a recombinant protein by using said host cell.

The claims encompass various nucleic acids having unknown nucleotide sequences adding to 5', 3' and/or within the sequence of SEQ ID No. 1 or 2, or a nucleotide sequence encoding SEQ ID No. 3. The specification of the present application only disclosed the nucleotide sequences of SEQ ID Nos. 1 and 2 (rat semaphorin) and the amino acid sequence deduced from SEQ ID No. 2 (SEQ ID No. 3), and the nucleotide sequences of human semaphorin cDNA (SEQ ID Nos. 4, 5, 7 and 10).

The scope of the claims include various unknown and unidentified nucleic acids encoding a genus of numerous structural variants, derived from different organisms including humans, cows, dogs, mice, whales, fish, insects, plants etc., of the disclosed semaphorin protein (SEQ ID No. 3), and the genus is highly variant because a significant number of structural differences between genus members is permitted. Nucleotide sequence of SEQ ID Nos. 1 and 2 contains 4008 bases and 2331 bases, respectively, and 20% variation of SEQ ID Nos. 1 and 2 would account for about 800 bases and 466 bases differences, respectively. The claimed nucleic acids could vary dramatically from the disclosed nucleotide sequences of the present application and the amino acid sequences encoded by said nucleic acid also could vary dramatically.

The specification fails to provide adequate guidance for a domain or a region within a semaphorin that contributes to any functional characteristic of the semaphorin having the sequence of SEQ ID No. 3 other than the proposed amino acid residue at position 204 of SEQ ID No. 3 and somaphorin domain. There is no indication of regions or specific amino acids within the semaphorin where mutations or variations would be tolerated without any change of the functional characteristic of the semaphorin and regions where they would not be tolerated other than the proposed amino acid residue at position 204 of SEQ ID No. 3. The amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Rudinger, 1976 (W) points out that

"The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) discloses that a single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding (e.g. title). Therefore, one skilled in the art at the time of the invention would not be able to predict the function of a protein merely from the amino acid sequence of said protein. In view of such, the unpredictability of the biological function of a protein, and the lack of detailed information regarding the structural and functional requirements of a semaphorin, it would be unpredictable at the time of the invention whether the proteins encoded by the claimed nucleic acids would still retain the functional characteristic of the amino acid sequence of SEQ ID No. 3.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and the breadth of the claims that one skilled in the art at the time of the invention would have had to engage in undue experimentation to practice over the full scope of the invention claimed.

It should be noted that unpredictability of biological function of a protein from mere amino acid sequence according to the state of the art is sufficient to render one skilled in the art at the time of the invention undue experimentation to practice over the full scope of the invention claimed.

Applicants argue that "unpredictability" alone does not establish undue experimentation and other wands factors are required for determining enablement of a claimed invention, and the claims include limitation of biological activity of the protein (amendment, page 18). Applicants further argue that methods of making mutation and screening variants of sequences representing claimed functional embodiment are known and predictable, and screening for hybridomas described in the Wands case is not undue experimentation (amendment, p. 18-19). This is not found persuasive because of the reasons set forth above in the 112 first enablement section and that the state of the art of amino acid sequence-protein function correlation indicates that protein function is unpredictable by mere amino acid sequence of said protein. It is not sufficient for one skilled in the art to predict the biological function of a semaphorin protein merely by its amino acid sequence. Sufficient structural features that contribute to the biological function of a semaphorin protein are still lacking. Screening hybridoma is a different subject matter from predicting protein function and the lack of undue experimentation for screening hybridoma does not necessarily mean that predicting protein function from its amino acid sequence does not require undue experimentation. Unpredictability of protein function from mere amino acid sequence according to the state of the art at the time of the invention is sufficient to establish that undue experimentation is required to practice over the full scope of the invention claimed.

Conclusion

Claims 43, 45 and 48-50 are rejected. Claims 34, 41, 42, 51 and 52 are in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Kimberly Davis, whose telephone number is (703) 305-3015.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.